REMARKS

Claims 10, 13-16, 19-26, and 36-44 are pending and appear in this application for the Examiner's review and consideration. Of these, claims 10, 13-14, 16, 19, 21-24 are currently amended and claims 36-44 are new. Claims 1-9, 11-12, 17-18, and 27-35 are cancelled. Claim 10 is amended as being drawn to a pharmaceutical composition comprising an isolated peptide according to an embodiment of the invention, and to correct typographical errors. Claims 13, 14, 16, and 22-24 are amended to correct dependency and/or for consistency. Claims 19 and 21 are amended for clarity. New claims 36-44 are added as being directed to embodiments of the invention. Support for these amendments is found throughout the specification, for example, at p. 2, line 24 to p. 4, line 22; p. 3, line 1 to p. 4, line 26; p. 7, lines 1-9; p. 8, lines 9-20; and p. 13, lines 13-15. Support for the corrections in sequence numbers in claim 10 is also found in the Sequence Listing. As no new matter is added, entry of the amendments at this time is respectfully requested.

The amendments to the claims are being made solely to expedite prosecution of the present application and do not constitute an acquiescence to any rejection by the Examiner. Applicant reserves the option to further prosecute the same or similar claims in the present or a subsequent application.

Sequence Compliance

The application is objected to for not including a SEQ ID NO in the pages noted by the Examiner. In response, the specification is amended to include the SEQ ID NOS of the corresponding amino acid sequences. With respect to the Examiner's referenced to the sequence N-CBZ-PRO-Leu-Gly-Hydroxamate on page 18, line 21 of the specification, Applicant respectfully submits that the sequence includes less than four amino acid residues and therefore does not require a SEQ ID NO. The Sequence Listing is also amended with corresponding changes, and a Substitute Sequence Listing is submitted herewith in paper and computer readable form copies.

Claim Rejections -- 35 U.S.C. § 112

Claims 1-35 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement for the reasons stated on pages 2-5 of the Office Action. Claims 1-35 are also rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for

the reasons stated on pages 5-9 of the Office Action.

Applicant respectfully submits that these rejections are moot in view of the claim amendments. As amended, the pending claims are directed to a pharmaceutical composition comprising as an active ingredient a peptide selected from the group consisting of SEQ ID NOS: 1-2, 4-8, 10-14, and their analogs, homologs or derivatives; a method for protecting or treating an individual against noxious stimuli or inflammatory processes by administering a therapeutically effective amount of such pharmaceutical composition; a peptide selected from the group consisting of SEQ ID NOS: 1-2, 4-8, 10-14, and their analogs, homologs or derivatives; and a method for treating a degenerative disease or a tumor in an individual by administering such peptide or a pharmaceutical composition comprising as an active ingredient human fibrinopeptide A of SEQ ID NO:9. All of the recited amino acid sequences, as well as their uses in treating or protecting against noxious stimuli or inflammatory process or in treating a degenerative disease or a tumor, are expressly disclosed in the specification (see, e.g., pp. 2-8). Further, given the disclosure of the specific sequences and their uses, a person having ordinary skill in the art will be able to make and utilize the sequences. Accordingly, Applicant respectfully submits that the pending claims meet the written description and the enablement requirements.

Claims 11, 12, 29, and 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Since these claims are cancelled, the rejection is moot.

Claim Rejections -- 35 U.S.C. § 102

Claims 1-5, 7-12, 16-30, and 32-35 are rejected under 35 U.S.C. § 102(a) as being anticipated by Y. Masuda and T. Sugiyama (*Peptides* 22:1511 (2001)); under 35 U.S.C. § 102(b) as being anticipated by Scherer et al. (*Clin. Exp. Immunol.* 40:49 (1980)); under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,468,537 to Datta et al.; and under 35 U.S.C. § 102(e) as being anticipated by U.S. Publication No. US 2004/0039157 to Staton et al. Applicant respectfully traverses all of these rejections.

Masuda discloses that administration of human fibrinopeptide A to mice can reduce excessive allergic reaction. Scherer relates to the administration of human fibrinopeptide A and B to treat experimental allergic encephalomyelitis and their mechanism of action. While these references disclose SEQ ID NO: 9, the references do not disclose or suggest any of the sequences

recited in the present claims or uses thereof. In particular, because Masuda and Scherer each relate only to human fibrinopeptide A, they do not disclose or suggest the peptide analogs of guinea pig Fibrinopeptide A as set forth in SEQ ID NO:2 and SEQ ID NO:4.

Accordingly, the rejections over Masuda and Scherer should be withdrawn.

Datta discloses pharmaceutical compositions comprising histone H2A peptide fragments including a 15-mer peptide of the sequence LRKGNYAERVGAGAP, and the administration of these peptides for the treatment of systemic lupus erythematosus.

Applicant respectfully notes that the isolated peptides disclosed in Datta correspond to the amino acid sequence of a portion of a nucleosome histone protein, which is capable of promoting immunological tolerance in an animal having systemic lupus erythematosus. Histone H2A is identified among the nucleosome histone proteins, and Datta discloses that, out of a large array of overlapping 15-mer peptides spanning all of the core protein histone H2A, peptide H2A 34-48 is capable of stimulating IL-2 production in CD4+ T cells derived from SLE patients (see FIG. 14A; col. 43, lines 14-28). However, none of the adjacent 15-mer peptides, for example, H2A 31-45 and H2A 37-51 peptides, was found to be effective in inducing IL-2 production in CD4+ T cells derived from SLE patients in Datta (see FIG. 14A). In fact, according to Datta, H2A 34-48 was the only 15-mer peptide found to be capable of promoting immunological tolerance in an animal having SLE (see FIG. 21; col. 45, lines 17-27). Thus, there is no disclosure or suggestion in Datta of a 9-mer peptide corresponding to the amino acid sequence 36-44 of H2A, which is capable of protecting against or treating inflammation or inflammation-related diseases and noxious stimuli. Moreover, in FIG. 17A, which localizes specific regions within the isolated histone peptides that are responsible for the stimulatory effect on IL-2 production in CD4+ T cell lines derived from SLE patients, the region H2A 34-38 is identified as the stimulatory region of the H2A 34-48 peptide. Hence, Datta does not disclose or suggest the 9-mer peptides corresponding to the amino acid sequence 36-44 of human H2A.

In addition, Applicant has performed an experiment to show that, in contrast to the 15-mer peptide H2A 34-48 consisting of the amino acid sequence LRKGNYAERVGAGAP, which is ineffective in treating experimental autoimmune encephalitis (EAE) in mice, the 9-mer peptide designated as 3m1 in this application, consisting of the amino acid sequence KGHYAERVG of SEQ ID NO:13 (see p. 3, line 30), surprisingly and significantly reduced the development of

EAE in mice. The EAE is an animal model for multiple sclerosis. The results of the experiment are graphically illustrated in a graph entitled "Effect of H2A 34-48 on EAE," attached hereto as Exhibit A.

In this experiment, mice were immunized subcutaneously with myelin oligodendritic glycoprotein (MOG) and injected intraperitoneally with pertusis toxin (PTX) immediately thereafter. Additional PTX was injected two days later. Each peptide was orally administered 4 (the day of onset of neurological symptoms), 7, 9, 11, 14, and 16 days after MOG immunization at a dose of 10 mg/kg for 3m1 (designated in the graph as "IIIM1") and 15 mg/kg for H2A 34-48 for each administration, while only the saline vehicle was administered to the control group. The doses were equivalent to 10 μmole/kg for both peptides. The time of administration is shown by arrows on the attached graph. The animals were scored for a neurological score ranging from 0 (no effect) to 4 (severe neurological symptoms including paralysis). The results are shown on the graph as the mean ± SE (n=10 animals for all groups except for control, for which n=11).

The results show that histone peptide H2A 34-48 was ineffective in preventing the development of neurological symptoms in mice, while peptide 3m1 was highly effective. These results further demonstrate that the disclosure relating to H2A 34-48 in Datta does not anticipate the 3m1 peptide, their analogs, and their uses in treating or protecting against noxious stimuli and inflammatory conditions such as multiple sclerosis.

Further experimental results for the claimed peptides in treating arthritis, EAE, and inflammatory conditions are also shown in Applicant's International Publication No. WO 2005/090387, entitled "Histone H2A Peptide Derivatives and Analogs and Methods of Use Thereof." Examples 13 to 17 of this publication are attached hereto as Exhibit B.

Accordingly, the rejection under 35 U.S.C. § 102(e) over Datta should be withdrawn.

The rejection over Stanton should also be withdrawn. Staton relates to the administration of a 24-mer peptide ADSGEGDFLAEGGGVRGPRVVERH for the treatment of tumors. The Examiner indicates that this peptide is a homolog and/or analog of the fibrinopeptide A peptides of this application, specifically SEQ ID NO: 2, 4, 9, and 11 (see Office Action, p. 12).

Staton, however, shows that the 24-mer peptide disclosed in the reference is *anti-*

angiogenic, while a shorter peptide designated Fibrin E-fragment, consisting of 16 amino acid residues of the sequence ADSGEGDFLAEGGGVR, is pro-angiogenic (see ¶ [0099]). Thus, Staton does not disclose or suggest the anti-angiogenic effect of human or guinea pig fibrinopeptide A or analogs thereof consisting of 12 to 15 amino acid residues. In contrast, human Fibrinopeptide A, a 15-mer peptide having the amino acid sequence ADSGEGDFLAEGGGV of SEQ ID NO:9, and guinea pig Fibrinopeptide A peptide or analogs thereof of SEQ ID NOs:2, 3, and 4, consisting of 12 to 14 amino acid residues each, have been surprisingly found by Applicant to be useful for preventing or treating malignant or benign tumors. Thus, Stanton does not anticipate the present claims.

Therefore, Applicant respectfully requests that all rejections under 35 U.S.C. § 102 be withdrawn.

In view of the above, the entire application is believed to be in condition for allowance, early notification of such would be appreciated. Should the Examiner not agree, a personal or telephonic interview is respectfully requested to discuss any remaining issues in order to expedite the eventual allowance of the claims.

Respectfully submitted,

Date 8/30/06

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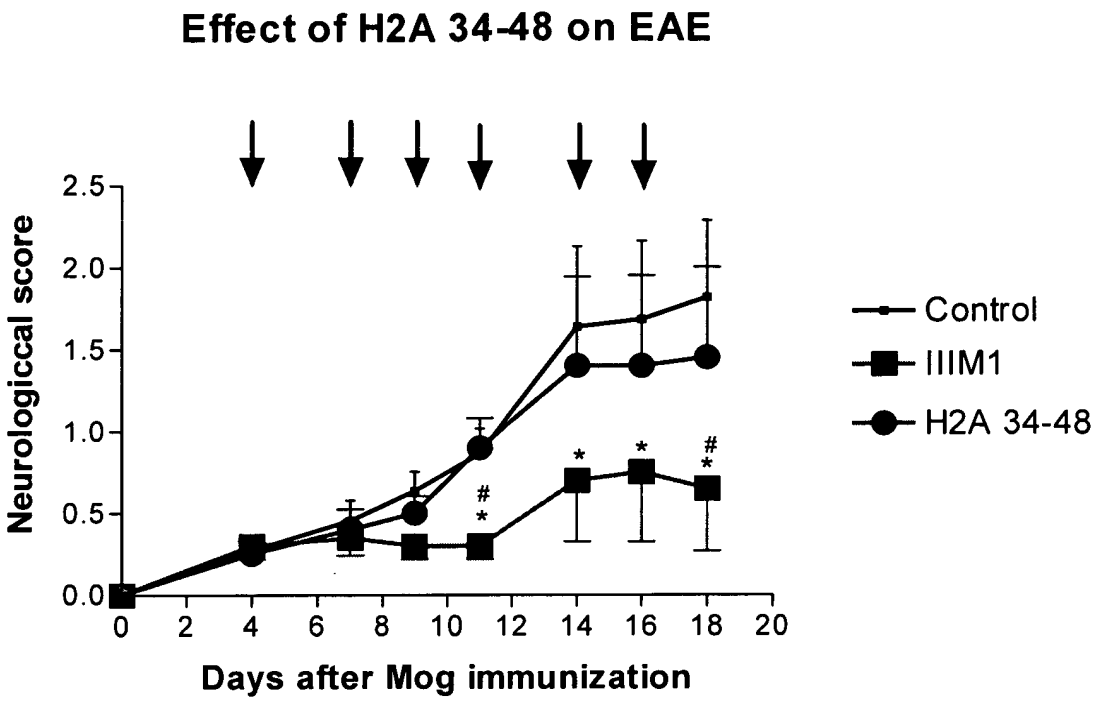
EXHIBIT A



*p<0.02 IIIM1 vs Cont

#p<0.05 IIIM1 vs H2A 34-48

Table 3: Elution profile of a mixture of cobalt chloride and IIIM1.

	Retention time	Peptide content	Cobalt content
Peak I	18.2	IIIM1	<0.5 µg/l
Peak II	19.1	IIIM1	7.5 µg/l

EXAMPLE 12

Effect of III and IIIH peptides on SM-induced skin lesions in guinea pigs

Male guinea pigs were intracadially injected with either peptide III (SEQ ID NO:2), IIIH (SEQ ID NO:31) or IIIU3 (SEQ ID NO:29; 1 mg of each peptide/kg) or the vehicle (0.9% NaCl) either 7 days (single treatment; FIG. 11A) or 7, 5, 3 days and 20 min (total of 4 injections; FIG. 11B-C) prior to exposure to sulfur mustard (SM). The backs of the animals were shaved 24 hours prior to the exposure, each back was divided into six sites, each site was exposed to 1µl (1.27 mg) of SM. The size of ulceration area of each exposure site was measured and expressed as squared mm. Results are the mean ±SE of 18 sites in the control group and 18 sites in the peptide-treated groups.

As shown in FIG. **11A-C**, pretreatments of guinea pigs with peptide III resulted in statistically significant protection (*$p<0.05$, Mann-Whitney test) against SM-induced skin lesions. Peptides IIIH and IIIU3 showed protective effect against SM-induced skin lesions, though it was less prominent.

EXAMPLE 13

Effect of peptide IIIM1 on arthritic mice

Collagen of bovine tracheal cartilage (1.8 mg) was incubated overnight in 0.01 M acetic acid (0.9 ml) at 4° C. The resulting solution was emulsified with equal volume (0.9 ml) of Complete Freund's Adjuvant. Fifty microliters of the emulsion were injected intradermally in the tail base of a mouse. The immunization was repeated 25 days later. The joints started to swell 5 days after the second immunization. On the same day, IIIM1 peptide was injected intracardially (1 mg/kg in 0.25 ml saline). IIIM1 peptide injection was repeated 7, 11 and 14 days after the first peptide injection. Degree of joint swelling was

calculated as the difference in joint thickness between the indicated time intervals and prior immunization. Results are the mean ±SE of 18 joints of each experimental group using the Mann Whitney test for evaluation of the differences between the peptide-treated and control groups.

As shown in FIG. **12**, IIIM1 peptide was very potent in reducing joint swelling.

EXAMPLE 14

Effect of IIIM1 and IIIH peptides on experimental autoimmune encephalitis in female mice – a model for multiple sclerosis

Female C57BL mice were intracardially injected with 1 mg/kg IIIM1 peptide (n=6) or IIIH peptide (n=5) or the vehicle NaCl 0.9% (n=6) (volume of injection - 0.25 ml/animal) under light pentobarbital (15 mg/kg) anesthesia. Immediately thereafter myelin oligodendritic glycoprotein (MOG) 35-55, emulsified with Complete Freund's Adjuvant, was subcutaneously administered into 4 sites on the back, adjacent to each of the forelimbs and hindlimbs, each injection was at volume of 50 µl. Each animal was i.p. injected with pertusis toxin in PBS (200 ng/mouse). The pertusis toxin injection was repeated after 2 days. The animals were evaluated for neurological score from 0 (no effect) to 4 (severe neurological symptoms including paralysis). Results are the mean±SE of neurological score (sum of all scores divided by the number of animals in each experimental groups) at each of the indicated time intervals after immunization.

FIG. **13** shows the anti-multiple sclerosis effect of IIIM1 peptide and, to a lesser extent, of IIIH peptide.

EXAMPLE 15

Effect of IIIM1 peptide on experimental autoimmune encephalitis in male mice – a model for multiple sclerosis

Male C57BL mice were intracardially injected with 1 mg/kg IIIM1 peptide (n=7) or the vehicle NaCl 0.9% (n=7) (volume of injection - 0.25 ml/animal) under light pentobarbital (15 mg/kg) anesthesia. Immediately thereafter, MOG 35-55 emulsified with Complete Freund's Adjuvant was subcutaneously administered into 4 sites on the back,

adjacent to each of the forelimbs and hindlimbs, each injection was at volume of 50 µl. Each animal was i.p. injected with pertusis toxin in PBS (200 ng/mouse). The pertusis toxin injection was repeated after 2 days. The animals were evaluated for neurological score from 0 (no effect) to 4 (severe neurological symptoms including paralysis). Results are the mean±SE of neurological score (sum of all scores divided by the number of animals in each of the experimental groups) at each of the indicated time intervals after immunization.

FIG. **14** shows the anti-multiple sclerosis effect of peptide IIIM1.

EXAMPLE 16

Effect of IIIM1 peptide on carrageenan-induced inflammation in mice

Peptide IIIM1 or its vehicle - saline, was injected 7, 5, 3 days and 20 min prior to carrageenan treatment. Carrageenan (50 µl of 3 mg/ml) was injected into the subplantar area of both limbs of each animal. The diameter of the subplantar area was measured every 60 min by a micrometer. The degree of swelling was assessed by the difference between thicknesses measured after and prior to carrageenan injection. Each group (peptide and control) contained 8 mice, namely, 16 limbs.

FIG. **15** clearly shows the anti-inflammatory effect of IIIM1 peptide.

EXAMPLE 17

Effect of IIIH and IIIM1 peptides on carrageenan-induced inflammation in male rats

Peptides or their vehicle - saline, were injected 7, 5, 3 days and 20 min prior to carrageenan treatment (volume of injection 0.25 ml). Carrageenan (100 µl of 1%) was injected into the subplantar area of both limbs of each animal. The diameter of the subplantar area was measured every 60 min by a micrometer. The degree of swelling was assessed by the difference between thicknesses measured after and prior to carrageenan injection. Each group (IIIM1 (n=10), IIIH (n=10) and control - 0.9% NaCl (n=8)) was treated as described.

FIG. **16** clearly demonstrates the anti-inflammatory effect of IIIH peptide and IIIM1 peptide in male rats.